

Applicants : John H. HEALEY and Gene K. DIRESTA  
U.S. Serial No.: 09/890,116  
Filed : July 26, 2001  
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#### REMARKS

Claims 38-76 are pending in this application.

Applicants have proposed herein above to amend claims 38 and 54. Support for amended claim 38 may be found inter alia in the specification at page 8, lines 15-16 (disclosing that a bone cement, such as a polymethyl methacrylate (PMMA) bone cement, useful as a local drug-delivery system for an anti-resorption agent) and at page 17, lines 23-24 (disclosing that the anti-resorptive agent's particle-size is about the same or less than the size of the bone-cement's particles). Support for claim 54 may be found inter alia in the specification at page 17, lines 29-30 (disclosing that the anti-resorptive agent sufficient to prevent loosening of the bone cement from the living bone to which it is attached for an extended period of time). Accordingly, there is no issue of new matter and Applicants request that amended claims 38 and 54 be entered in this application. Upon entry, claims 38-76 are pending.

#### Claim Rejections - 35 USC §103

The Examiner rejected claims 38-53 under 35 U.S.C. 103(a) as being unpatentable over Anuta U.S. Patent No. 4,341,691 and Lehtinen U.S. Patent No. 5,733,564 A. in view of Remington's Pharmaceutical Sciences. The Examiner further rejected 54-76 under 35 U.S.C. 103(a) as being unpatentable over Mao et al. U.S. Patent No. 6,238,687 B1 and Gayer et al U.S. Patent No. 6,214,049 B1.

In response, Applicants' undersigned attorney had a telephone conference with the Examiner assigned to this matter. Examiner invited the Applicants' rebuttal to Remington's Pharmaceutical Sciences.

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The particle size issue that Remington's article addresses relates to the blending of separate powder components of a formulation to ensure uniformity and minimize demixing. Applicants would note that, on settling larger particles tend to rise to the surface, the opposite of what Remington's article states.

The particle size phenomenon has been studied at length by many groups. It is referred to as "Vibration Induced Particle Segregation". The effect referred to as the 'Brazil - Nut" or "Muesli Effect". Applicants hereto attach article, Matthias, et al., Brazil-nut effect: Size Separation of granular particles, Nature 414, 270 (2001); doi:10.1038/35104687 as Exhibit 1 (3 pages). In Matthias, et al. it is noted that "unlike two-fluid systems, bi-disperse granular mixtures will separate according to particle size when shaken, with large particles rising".

Further, Applicants hereto attach a study of Computational Fluid Dynamics as Exhibit 2 (2 pages). The study indicates "As the shaking occurs, short lived gaps are created in the microstructure, allowing small particles to fall to lower levels. The intrusion of smaller particles prevents the larger particles from returning to their previous packed state."

The intent of the Applicants' claimed invention is to ensure that the particle distribution with the polymerized material placed against the bone will maximize the quantity of drug positioned against the bone. Remington addresses the uniformity of drug within powder during blending prior to packaging (gram drug/gram blend) but does not address the issue of quantity of drug in direct contact with bone (gram drug/polymerized cement-drug surface area).

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Further, regardless of the particle size of drug within the cement, once the cement-drug powder is combined with the monomer catalyst, a viscous suspension of cement and drug is formed that becomes uniformly blended and separation associated with particle size can no longer occur because the viscous solution, by virtue of polymerization, becomes a dough and finally a solid. Thus a large particle drug will be uniformly distributed within the cement during the mixing with monomer. However, drug content of solid per exposed surface area is a function of particle size. The smaller the particle size the more drug available for contact with bone.

Applicants believe that the above arguments address Remington's particle size issue and respectfully request the reconsideration and withdrawal of all ground of rejections.

If a telephone interview would be of assistance in advancing prosecution of the subject application, Applicants' undersigned attorney invites the Examiner to telephone at the number provided below.

No fee other than the \$55.00 Petition to Request One-Month Extension fee is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 50-1891.

Respectfully submitted,

Albert Wai Kit Chan

Albert Wai-Kit Chan  
Registration No. 36,479  
Attorney for Applicants  
Law Offices of  
Albert Wai-Kit Chan, LLC  
World Plaza, Suite 604  
141-07 20<sup>th</sup> Avenue  
Whitestone, New York 11357  
Tel: (718) 357-8836  
Fax: (718) 357-8615  
E-mail: kitchanlaw@aol.com